Appellants' Brief Under 37 C.F.R. § 1.192
Application No. 08/716,169
Reply to Office Action dated November 25, 2002
Paper dated August 25, 2003
Attorney Docket No. 0470-961125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	08/716,169
Applicants	:	Stephen M. Anderton et al.
Filed	:	December 17, 1996
Title:	:	Peptide Fragments of Microbial Stress Proteins and Pharmaceutical Composition Made Thereof for the Treatment and Prevention of Inflammatory Diseases
Group Art Unit	:	1644
Examiner:	:	Patrick J. Nolan, Ph.D.
Docket No.	:	0470-961125

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
P.O. Box 1450
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

This appeal brief is in support of the Notice of Appeal filed March 25, 2003.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 25, 2003.

Anna Rosenstein
(Typed Name of Person Mailing Correspondence)

Anna Rosenstein 8/25/2003
Signature Date

{W0076524.1}

I

REAL PARTY IN INTEREST

Universiteit Utrecht is the Assignee of the entire right, title, and interest to the above-identified application and, as such, is the real party in interest in this Appeal.

II

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants, the Appellants' legal representative, or the Assignee of the above-identified application which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III

STATUS OF CLAIMS

Of claims 1-30, claims 1-23 are cancelled and claims 24-30 are appealed.

Claims 24-30 are reproduced in Appendix A which is attached hereto.

IV

STATUS OF AMENDMENTS

All claim amendments have been entered on the application.

V

SUMMARY OF THE INVENTION

The invention generally pertains to peptides containing a part of the amino-acid sequence of a mammalian stress protein having conserved homologues in microorganisms and mammals, which peptides are able to treat inflammatory disease. The claimed invention is thus a method of treating inflammatory disease by administering a particularly defined peptide in an effective amount. The peptide so defined has 7-30 amino acids and contains specified identical and consecutive amino acids to constitute a T cell epitope corresponding to a T cell epitope of a conserved mammalian stress protein homologue from a microbial protein. The ability of the administration of such peptides to reduce the effects of inflammatory disease has already been shown of record by means of data and expert testimony.

VI

ISSUES PRESENTED

Whether Appellants have met the enablement requirement of 35 U.S.C. Section 112, first paragraph, to show the predictability of selecting peptides according to the invention in order to treat mammalian inflammation.

VII

GROUPING OF CLAIMS

The appealed claims stand or fall together.

VIII

ARGUMENT

35 U.S.C. Section 112, first paragraph

After a lengthy prosecution, the only issue which remains for resolution is an asserted rejection under 35 U.S.C. Section 112, first paragraph. In the Office Action dated November 25, 2002, the Examiner asserts that claims 24-30 do not meet the 35 U.S.C. Section 112, first paragraph requirement of enablement. The Examiner asserts that enablement has been established only against experimentally induced adjuvant arthritis or atherosclerosis. The Action asserts that Anderton et al., "Peptide-based immunotherapy of autoimmunity: a path of puzzles, paradoxes and possibilities," Immunology, vol. 104, pp. 367-376 (2001) and Wendling et al., "A conserved mycobacterial heat shock protein (hsp) 70 sequence prevents adjuvant arthritis...," The Journal of Immunology, vol. 164, pp. 2711-2717 (2000) (both representing the later published work of two of the present co-inventors) call into question the predictability of the animal model data with respect to human treatment.

Appellants respectfully submit that the asserted enablement rejection is in condition to be reversed, both because appropriate legal precedent does not permit an enablement rejection to hinge on articles published after the priority date, and even if it did in the instant case the later publications are consistent with the present claims and inventors' representations anyway. In view of the more detailed explanation provided below, reversal of the sole remaining enablement rejection in the above-identified patent application is therefore respectfully requested.

As summarized above, the invention is a method of treating inflammatory disease

by administering a particularly defined peptide in an effective amount. The peptide has 7-30 amino acids and contains specified identical and consecutive amino acids to constitute a T cell epitope corresponding to a T cell epitope of a conserved mammalian stress protein homologue from a microbial protein. However, such a short summary belies the detail with which the inventors disclosed the specifics of the anti-inflammatory peptides. The present specification goes into extensive detail regarding the various amino acid sequences of the underlying heat shock proteins, thus guiding one skilled in the art to the selection of the claimed peptides. The specification also discloses a variety of tests conducted to confirm the inventive peptides' abilities to provoke an anti-inflammatory response, and the results of those tests. The Board's attention is directed, in particular, to the Results section of the specification, pages 7-23, which not only goes into detail regarding the applicable amino acid sequences of the present invention but also documents that lymph node responses to administration of the inventive peptides established anti-inflammatory data pertinent beyond the treatment of mere experimentally induced adjuvant arthritis or atherosclerosis. As a separate matter, this same section of the specification also documents the **inability** of similar peptides from non-microbial proteins to create the same anti-inflammatory effect of the claimed peptides. The Board will appreciate when reviewing pages 7-23 of the specification, which review is respectfully requested, that the extensive sequence disclosure and data in the specification alone underscore the enablement of the claimed peptides and their anti-inflammatory effects.

Additional mammalian data are already of record to provide objective corroboration that the claimed peptide was able to inhibit progression of atherosclerotic regions

in mice and would thus be appreciated to have anti-inflammatory effects generally. The Declaration of Professor Willem van Eden dated November 9, 2002, already of record, presents and explains its attached Exhibit, which Exhibit shows by bar graph that atherosclerotic lesion (plaque) inhibition by the inventive peptides myc-HSP60 and pept253-268 occurred in contrast with control proteins SOD and pept B23. Not insignificantly, the Exhibit also shows that the inventive peptides demonstrated about the same plaque inhibiting activity as did the comparative administration of oxidized low density lipoprotein, a well-known atherosclerosis inhibitor. As Dr. van Eden concludes in view of the data, in his Declaration, Paragraph 6, the representations of the above-identified patent application as to efficacy are accurate, corroborated and described in such a way as to enable one skilled in the art to practice the invention disclosed and claimed. This expert opinion of Professor van Eden, namely, that the disclosed invention is enabled, is entitled to greater weight than any unsupported assertions in the November 25, 2002 Office Action.

Neither Anderton et al., "Peptide-based immunotherapy of autoimmunity: a path of puzzles, paradoxes and possibilities," Immunology, vol. 104, pp. 367-376 (2001) nor Wendling et al., "A conserved mycobacterial heat shock protein (hsp) 70 sequence prevents adjuvant arthritis...," The Journal of Immunology, vol. 164, pp. 2711-2717 (2000), should be considered at all with respect to enablement, because each was published subsequent to the instant priority date. Appellants have satisfied the test of In re Wright, 999 F.2d 1557, 27 U.S.P.Q. 2d 1510 (1993), by having provided significantly in excess of one working example, as well as much comparative data to support a broad scope of enablement. Thus In re Hogan,

559 F.2d 595, 194 U.S.P.Q. 527 (1977) continues to apply, and publications which are not prior art are also not properly citable for enablement purposes.

Even if the Anderton et al. and Wendling et al. references were to be considered by the Board, however, they are not inconsistent with and are actually supportive of the positions Appellants have taken throughout the prosecution of the instant case. Upon consideration of the below analysis, it is believed that the Board will conclude that neither Anderton et al. nor Wendling et al. call enablement into question.

The Anderton et al. reference is directed to assessing the prospects of using synthetic peptide antigens, and specifically altered peptide ligands (APLs), **to target pathogenic T cell autoreactivity**. This means that artificially altered peptides are used either to silence such pathogenic T cells or to switch the phenotype of such T cells to a less pathogenic one. The authors' conclusion is that although such effects can be obtained on specific T cell lines *in vitro*, the altered peptides on the other hand unfortunately may induce and activate other T cells (with other fine specificities) *in vivo* so that at least some of the time the altered peptides can appear to be autoreactive and pathogenic. Therefore, Anderton et al. favor an alternate approach instead: the use of natural peptide sequences to tolerize the immune system, preferably by expansion of self-reactive T regulatory cells capable of bystander suppression, see concluding remarks, page 373.

By contrast, the present claims are not directed to targeting pathogenic T cells. The emphasis on pathogenic T cells can be seen throughout Anderton et al., including the reference to pathogenic T cells in the Introduction. However, the claimed peptides are discussed

in the specification as inducing and in fact do induce regulatory T cells specific for heat shock protein. Because the expression of heat shock protein is enhanced in inflamed tissue, such induction of regulatory T cells is ideal to treat inflammation. In other words, neither the specification nor claims ever suggested that the phenotype of existing, pathogenic T cells could be altered: the inventive peptides induce regulatory T cells *de novo* and the induced T cells combat the inflammation. Thus there is nothing inconsistent in Anderton et al. with respect to the present invention.

The Examiner has cited a particular passage in Anderton et al., at page 370, column 2, first paragraph, as supporting the unpredictability of APL in autoimmune disorders, however this passage must be understood in context. APL is an abbreviation defined, at page 367 of Anderton et al., to mean, "altered peptide ligand," and thus is a term of generic-type breadth as contrasted with the specific invention as claimed. The Anderton et al. article discusses many different peptides and many different epitopes, without focussing on the microbial heat shock proteins of the present invention. The fact that Anderton et al. identify a variety of APLs, other than the inventive peptides, which do not behave predictably only underscores the significance of the present specific treatment method, which was disclosed in detail and exhaustively corroborated. No enablement rejection should hinge on Anderton et al., therefore, even if the Anderton et al. reference is somehow considered to be properly citable.

Regarding Wendling et al., the Appellants wish to point out that the present specification was written and filed on the order of ten years ago, and at that time nasal administration of peptides was in its infancy and thus not specifically mentioned. However, the

Wendling et al. disclosure of a mere one formulation that was unsuitable for parenteral administration does not impugn all possible parenteral formulas, which can be developed within the skill of the art. When one skilled in the art appreciates the key aspects of the invention—use of a peptide corresponding to the microbial peptide, not the mammalian one, and having the specified heat-shock-peptide type epitope—the administration of the claimed peptide can then be determined within a reasonable number of tries. Most importantly of all, however, one skilled in the art and practicing the claimed invention will certainly appreciate the value of nasal administration of peptides in a manner completely consistent with the disclosure of the invention in the first place. The invention inheres in knowing which peptide to administer, after all, not so much in how to do so.

IX

CONCLUSION

Because the Appellants disclosed their invention in detail, corroborated their assertions with data presented both in the specification and in the Professor van Eden Declaration, documented of record the supported conclusion of Professor van Eden that the claimed invention is enabled by the specification, and established why the Anderton et al. and Wendling et al. publications are consistent and supportive of the invention, reversal of the asserted lack of enablement rejection is respectfully requested.

Checks in the amount of $320.00 and $930.00 are enclosed to cover fees for the filing of the Appeal Brief and a three-month extension. The Commissioner for Patents and

Trademarks is hereby authorized to charge any additional fees which may be required to Deposit Account No. 23-0650. Please refund any overpayments to Deposit Account No. 23-0650. An original and two copies of this Appeal Brief are enclosed.

Respectfully submitted,

WEBB ZIESENHEIM LOGSDON
ORKIN & HANSON, P.C.

By _____

Barbara E. Johnson, Reg. No. 31,198
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219-1818
Attorney for Applicant
Telephone: (412) 471-8815
Facsimile: (412) 471-4094

APPENDIX A

24. A method of treatment of or protection against an inflammatory disease, including autoimmune diseases, such as diabetes, arthritic diseases, atherosclerosis, multiple sclerosis, myasthenia gravis, comprising administering an effective amount of a peptide of 7-30 amino acids having the sequence of a part of the amino acid sequence of a microbial protein having a conserved mammalian stress protein homologue, said part comprising a T cell epitope corresponding to a T cell epitope of the mammalian homologue, said part further comprising at least 5 amino acids which are identical with corresponding amino acids in the same relative position in a T cell epitope of said mammalian stress protein, said epitope and said part containing at least 4 consecutive amino acids which are identical with the corresponding mammalian stress protein amino acids and thereby forming said T cell epitope corresponding to a T cell epitope of a mammalian homologue.

25. The method of claim 24, wherein said stress protein is selected from heat-shock proteins and stress-induced enzymes.

26. The method of claim 25, wherein said heat-shock protein is heat shock protein hsp65 of *Mycobacterium tuberculosis* (identical to hsp65 of *M. bovis* BCG) as depicted in SEQ ID NO. 1.

27. The method of claim 26, wherein the peptide comprises at least 5 amino acids which are identical with the corresponding amino acids in the same relative position in one of the sequences 81-100 and 241-270 of SEQ ID NO. 1.

28. The method of claim 27, wherein the peptide comprises at least 5 amino acids which are identical with the corresponding amino acids in the same relative position in one of the sequences 84-95 and 256-265 of SEQ ID NO. 1.

29. The method of claim 24, wherein one or more of the amino acids residues has been exchanged with a residue of an amino acid having similar size, charge and polarity, or with amino acid mimetics resulting in one or more backbone modifications.

30. The method of claim 24, wherein said part does not contain one or more sections of 5-30 amino acids corresponding to T cell epitopes of said microbial protein, the T cell which epitope of said microbial protein having less than 4 consecutive amino acids which are identical with the corresponding amino acids of said mammalian stress protein amino acids, such that said peptide includes a microbial T cell epitope having sufficient sequence identity with a T cell epitope of said mammalian stress protein homologue and lacks any microbial T cell epitope which does not have sufficient sequence identity with corresponding amino acids of said mammalian stress protein homologue.